

Child, parent, and service predictors of psychotropic polypharmacy among adolescents
and young adults with an autism spectrum disorder

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Funding Sources: The Canadian Institutes of Health Research (funding reference number 102677) and the Centre for Addiction and Mental Health Postdoctoral Fellowship Award.

Final publication is available from Mary Ann Liebert, Inc., publishers
<http://online.liebertpub.com/doi/abs/10.1089/cap.2014.0011>

Abstract

Objectives: This study examined the child, parent, and service factors associated with polypharmacy in adolescents and young adults with ASD. **Methods:** As part of an online survey examining health service utilization patterns among individuals with ASD, parents provided demographic and clinical information pertaining to their child. This included information on current medication use, as well as information on clinical services received, clinical history, and parent wellbeing. Analyses examined the bivariate association between individual child, parent, and service variables and polypharmacy. Variables significantly associated with polypharmacy were included in a multiple variable logistic regression. **Results:** Of the 363 participants sampled, approximately one quarter were receiving two or more psychotropic drugs concurrently. The child's psychiatric co-morbidity, history of hurting others, therapy use, and parent burden were predictors of polypharmacy. **Conclusion:** Adolescents and young adults with ASD are a highly medicated population with multiple factors associated with psychotropic polypharmacy. While there may be circumstances where polypharmacy is necessary, a richer understanding of what predicts polypharmacy may lead to targeted interventions to better support these individuals and their families.

Findings also highlight the need to support families of children with ASD prescribed multiple psychotropic medications.

Key words: autism spectrum disorder; polypharmacy; psychotropic medication; adolescents; young adults

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Individuals with an autism spectrum disorder (ASD) are frequently prescribed psychotropic medications (Chen et al. 2011; Coury et al. 2012; Hsia et al. 2013; Langworthy-Lam et al. 2002; Logan et al. 2012; Mandell et al. 2008; Memari et al. 2012; Rosenberg et al. 2010; Schubart et al. 2012; Spencer et al. 2013), with as many as half taking two or more psychotropic drugs in adulthood (Esbensen et al. 2009; Lake et al. 2012). There are clearly circumstances where psychotropic medication use is warranted and necessary in this population, but its use is associated with a number of adverse effects including weight gain, sedation, irritability, tardive dyskinesia, and gastrointestinal problems (Matson & Hess 2011; McCracken 2005; Myers 2007). Long-term secondary effects include diabetes, cardiovascular disease, and hyperlipidemia (Posey et al. 2008; Stigler et al. 2004). These effects and the risk of adverse drug reactions and drug-drug interactions are heightened when multiple psychotropic medications are used (Lunsky and Elserafi 2012; Perkins and Berkman 2012; Schall 2002). Psychotropic polypharmacy, defined in this study as the concurrent use of two or more psychotropic medications in the same individual, while sometimes clinically indicated, is a recognized concern for individuals with ASD due to increased sensitivity to side effects and difficulties communicating and reporting their internal experience (Schall 2002).

To date, the majority of studies on psychotropic polypharmacy in individuals with ASD have been descriptive in nature (Aman et al. 2003; Aman et al. 2005; Khanna et al. 2012; Langworthy-Lam et al. 2002; Oswald and Sonenklar 2007; Tsakanikos et al. 2007; Witwer and Lecavalier 2005), with very few examining the factors associated with the

use of multiple psychotropic medications. Only four studies of children with ASD (Coury et al. 2012, Logan et al. 2012, Memari et al. 2012, Spencer et al. 2013) have examined factors associated with psychotropic polypharmacy, which have primarily focused on child demographic and clinical characteristics. Results of a large US study of 2,853 children and adolescents with ASD identified that greater age, Caucasian race, and non-Hispanic/Latino ethnicity were associated with the use of multiple psychotropic medications (Coury et al. 2012), along with gastrointestinal and sleep problems. In another large US study of 33,565 children with ASD, older children, those who had a psychiatric visit, those with co-occurring conditions, Hispanic children and those living in southern regions, had higher odds of polypharmacy (Spencer et al. 2013). Although age is positively related to psychotropic polypharmacy in youth with ASD (Coury et al. 2012, Logan et al. 2012, Memari et al. 2012, Spencer et al. 2013), only two studies have examined factors associated with psychotropic polypharmacy specifically among adolescents and adults with ASD. Findings from these studies suggest that greater age (Esbensen et al. 2009) and aggressive behaviour (Lake et al. 2012) predict the use of multiple psychotropic medications.

There may be other contributors to psychotropic polypharmacy, which are not associated with the individual with ASD's demographic or clinical presentation, but such variables have not been well studied. Utilization of non-pharmacological services (i.e., therapy, counseling, respite) and participation in structured daily activities (e.g., school, employment), may be important service variables to consider. One might expect that individuals who are unable to pay for medications would be less likely to use multiple psychotropic medications (Coury et al. 2012, Rosenberg et al. 2010), but the relationship

between psychotropic polypharmacy and availability and affordability of other types of services has not been studied. Parent circumstance may also play a role in prescription patterns. Research suggests that parents of children with ASD face significant caregiving burden (Cadman et al. 2009; Kring et al. 2008; Lin 2010), and that when families are in crisis they, and healthcare providers, may turn to medication as a solution (Mackintosh et al. 2012; Weiss et al. 2009). There are a number of possible parent factors that could contribute to this decision, including parent demographic variables (e.g., marital status, age, education) and parent psychological functioning (e.g., burden, crisis). Only two studies examined the relationship between polypharmacy and parent factors. In the first study, no association was observed between polypharmacy and poverty level, parent education or marital status (Memari et al., 2013). In the second study, household income, overall, was also mostly unrelated to polypharmacy (Spencer et al., 2013), but, no studies have considered the impact of other parent factors on psychotropic polypharmacy.

While there are ample data suggesting that psychotropic polypharmacy is a concern among individuals with ASD, our current understanding of what leads to its occurrence is based on an examination of limited variables. Most of the literature to date has examined the relationship between psychotropic polypharmacy and child variables such as demographic and clinical symptoms, with less emphasis on other important potential drivers like service and parent variables. Further, most studies tend to focus on children (e.g., Coury et al. 2012; Spencer et al. 2013) even though psychotropic polypharmacy is more common in older youth and adults. There is a critical need to study older youth and young adults because of difficulties encountered in the transition from adolescence to adulthood when changes to residence, education, and employment may

occur. Given our knowledge that individuals with ASD tend to reside with their parents well into adulthood (Howlin and Moss 2012), and that adolescents and young adults' with ASD have a high risk of psychotropic polypharmacy, it is important to have a more comprehensive understanding of the factors that contribute to its occurrence in this group. From a practice perspective, understanding more about the child, family, and service variables that increase the likelihood of psychotropic polypharmacy can improve patient-centered care and treatment planning. Findings can also inform ways to support families of individuals with ASD prescribed multiple psychotropic medications.

The current study addresses these gaps by examining the child, parent, and service variables associated with psychotropic polypharmacy in adolescents and young adults with ASD. Our study addresses the following objectives: 1) to determine the proportion of adolescents and adults taking two or more psychotropic medications 2) to identify the child, parent, and service variables associated with psychotropic polypharmacy.

Methods

The analyses reported here are based on data from a larger project examining health service utilization patterns among individuals with ASD. Parents of adolescents and young adults with ASD were recruited from educational, social service, recreational and mental health agencies and programs supporting people with ASD across Ontario.

As part of an online survey, parents completed demographic and clinical measures about their child including; service use, comorbid medical and psychiatric conditions, medication use, risk behaviours, severity of ASD, history of previous hospitalizations, and use of other health services. Parents also completed measures related to their own demographics (age, education, gender) and personal wellbeing (e.g., burden, crisis).

Clinical and parent items were largely obtained from previously validated measures (Mackintosh et al. 2012; Xiong et al. 2011), while demographic and utilization items were based on measures used in a previous study examining health service utilization patterns among individuals with developmental disabilities (Lunsky et al. 2012). Prior to launching the survey, measures were piloted among 10 families of adolescents and adults with ASD living in Ontario.

Materials/Procedure

As part of an online survey examining health service utilization patterns among individuals with ASD, parents provided demographic and clinical information pertaining to their child. This included information on current medication use, as well as information on clinical services received, clinical history, and parent wellbeing. Only individuals who exceeded the recommended research cut off on the SCQ (≥ 12) (44), a validated parent report instrument of autism severity were included in these analyses. All parents provided informed written consent after being provided with a detailed description of the study. This study received ethics approval through the relevant institution's institutional review board.

Study Variables

Child Variables

The following parent reported child variables were examined: age, gender, intellectual disability (ID), ASD diagnosis (autism, PDD-NOS, Asperger Syndrome), additional psychiatric diagnoses, history of hurting others, history of self-injury, and history of psychiatric admission. Individuals were classified as having ID if parents indicated that their child had a diagnosis of mild, moderate, severe, or profound ID.

Parent Variables

Parent variables included age, marital status, education, presence of another child with ASD, parent burden, parent crisis, and family counseling. Parent burden was assessed using the 9-item Caregiving Burden Scale (Lawton et al. 2000), and parent crisis using the Brief Family Distress Scale (BFDS; Weiss and Lunsky 2009). The Caregiving Burden Scale measures caregiver's appraisal of the physical, psychological, and social impact of caring for a child with ASD. Scores were categorized as low (<22), moderate (22–27) or high (>27) burden, as suggested by Pruncho and McMullen (2004). This measure has high internal consistency (Cronbach's $\alpha=0.87$) and acceptable stability (Lawton et al. 1989). Internal consistency of this measure in the current study was also high (0.92). The BFDS is a measure of perceived crisis in caregivers of individuals with ASD and consists of one item asking caregivers to rate on a scale of 1 to 10 where they and their family are currently in terms of crisis (Weiss and Lunsky 2011). Responses were dichotomized such that scores between 0 and 5 (i.e., no or moderate impairment) were classified as not currently in crisis and between 6 and 10 (i.e., marked impairment) as currently or approaching crisis. This scale has been shown to validly categorize families into groups based on their current crisis status (Weiss and Lunsky 2011). Family counseling was identified through parent report of family counseling services received in the previous two months. Parent education was dichotomized as high (college degree or higher) and low (high school or less).

Service Variables

We examined service affordability, structured daily activity, therapy use, and respite use. To measure service affordability, parents were asked: "Can your family

afford to pay for services that you need in your community?” Responses were dichotomized as caregivers who could afford services vs. caregivers who could not. Structured daily activities included the individual with ASD’s typical participation in any of the following for at least some part of the day: school, work, volunteer, job training, or day program. Responses were dichotomized as yes structured daily activity and no structured daily activity. Therapy use was defined by receipt of any of the following services in the previous two months: behaviour therapy, individual counseling or group therapy. Respite use was also defined by use in the past two months.

Outcome Variables

Medications were categorized into the following 11 medication classes for standard use: a) Psychotropic medications: antidepressants, anxiolytics, atypical antipsychotics, typical antipsychotics, stimulants, mood stabilizers, antihypertensives (e.g., clonidine); and b) Non-psychotropic medications: anticonvulsants, medications for gastrointestinal issues, medications for sleep issues (e.g., melatonin, zopiclone), and other non-psychotropic medications. Only antihypertensive medications which had evidence for the treatment of hyperactivity, inattention, or impulsivity, such as clonidine or guanfacine, (Arnsten et al. 2007; Posey et al. 2004) were categorized as psychotropic medication, as was done by others (Aman et al. 2003; Langworthy-Lam et al. 2002; Logan et al. 2012). Similarly, the distinction between mood stabilizers and anticonvulsants was made by classifying medications (e.g., valproate and carbamazepine) as mood stabilizers for all individuals who did not have a diagnosis of seizure disorder, as was done by others (Esbensen et al. 2009; Lake et al. 2012). Medication use was determined according to medications used regularly on the date of survey completion.

Psychotropic polypharmacy was operationalized as the concurrent use of two or more psychotropic medications in the same individual, either within or between therapeutic classes.

Data Analysis

Univariate statistics were used to describe demographic and medication information for the sample (numbers and percentages for count data and means and standard deviations for continuous variables). Bivariate analyses were used to analyze the association between individual child, parent, and service variables and ≥ 2 psychotropic medications (yes/no). Variables significantly associated with ≥ 2 psychotropic medications at or below $p \leq 0.05$ were included in a multiple variable logistic regression. Odds ratios with 95% confidence intervals were reported. Statistical analyses were conducted using SPSS version 20.0.

Results

Participant Characteristics

The current study examined medication profiles and predictors of medication use among parents of 363 adolescents and young adults with ASD. Individuals with ASD were between 12 and 30 years of age with a mean age of 17.30 ($SD = 4.01$). The majority of these individuals lived with family (338; 93%), over three quarters were male, and most were Caucasian (Table 1). Approximately one quarter of the sample (100; 27.6%) had a diagnosis of autism, 31.2% (113) were diagnosed with Asperger Syndrome, and 40.9% (148) were diagnosed with pervasive developmental disorder not otherwise specified (PDD-NOS) or ASD.

At the time of data collection, 182 of 363 (50.1%) adolescents and young adults were prescribed at least 1 psychotropic medication. See Table 2 for breakdown of

medication by class. The most commonly prescribed medication was antipsychotic medication, followed by antidepressant, and stimulant medications. Approximately one quarter (26.4%) of individuals were prescribed two or more psychotropic medications, and of those prescribed psychotropic medications, 13.2% were taking two or more psychotropic medications from the same therapeutic class (i.e., intraclass polypharmacy).

Child, parent and service factors associated with polypharmacy

Results of bivariate analyses for \geq two psychotropic medications are presented in Table 3. Child clinical variables significantly related to psychotropic polypharmacy were: history of hurting others ($p < 0.001$), history of self-injury ($p = 0.004$), history of psychiatric admission ($p < 0.001$) and having an additional psychiatric diagnosis other than an ASD ($p < 0.001$). No child demographic (e.g., age, gender, intellectual disability) variables were related to psychotropic polypharmacy. In terms of parent variables, family counseling ($p = 0.005$), having an additional child with ASD ($p = 0.037$), parent crisis ($p = 0.028$), and parent burden ($p = 0.036$), were significantly related to psychotropic polypharmacy. No parent demographic variables predicted polypharmacy. In terms of service use, only child therapy use (e.g., counseling, behaviour therapy) ($p < 0.001$) was significantly positively related to polypharmacy. That said, just over one third (37%) of those taking two or more psychotropic medications were not receiving any therapy services.

Prediction of polypharmacy: Multiple variable logistic regression analysis

Results of the logistic regression are summarized in Table 4. In the adjusted analysis, history of hurting others, having an additional psychiatric diagnosis, parent burden, and therapy use were significant predictors of psychotropic polypharmacy.

Specifically, adolescents and young adults with ASD with a history of hurting others were 2.7 times more likely to be prescribed two or more psychotropic medications than those without a history of hurting others. Similarly, adolescents and young adults with an additional psychiatric diagnosis were 2.4 times more likely to receive psychotropic polypharmacy than those without an additional psychiatric diagnosis. In terms of parent variables, parents reporting high levels of burden were 2.5 times more likely to be prescribed two or more psychotropic medications than parents who did not report high levels of burden. Finally, in terms of service use, adolescents and young adults receiving therapy were 2.8 times more likely to be prescribed two or more psychotropic medications than those not receiving therapy.

Discussion

This is the first study of adolescents and young adults with ASD to examine both demographic and clinical variables associated with multiple psychotropic medication use, and to consider the relative influence of parent and service factors. One quarter of adolescents and young adults with ASD were taking two or more psychotropic medications, and 13% of individuals taking two or more psychotropic medications were also taking psychotropic medications from the same therapeutic class (e.g., two antipsychotic, mood stabilizer or anxiolytic medications), which, according to prescribing guidelines for individuals with developmental disabilities, should be avoided (Posey et al. 2008; Reiss and Aman 1995; Sullivan et al. 2011). Psychotropic polypharmacy rates in this study, are similar to those observed in other clinical populations, including youth with symptoms of mania (Kowatch et al. 2013) and adults with schizophrenia or schizoaffective disorders (Goren et al. 2013). When all factors were considered, the main

contributors to psychotropic polypharmacy in the current study were history of hurting others, psychiatric comorbidity, parent burden and therapy service use. This would suggest that psychotropic polypharmacy is not only associated with the child's clinical presentation, but also with factors related to caregivers and service use.

Child Variables

In terms of child demographic variables, and contrary to what has been reported in previous studies (Coury et al. 2012; Esbensen et al. 2009; Logan et al. 2012; Memari et al. 2012; Spencer et al. 2013), age was not associated with psychotropic polypharmacy in the current study. There may be a few explanations for these differences with regard to age. Two of the aforementioned studies (Coury et al., 2012; Spencer et al., 2013) consisted of large samples, including young children of a broad age range. As a result, the power of these studies was greater and they may have been more likely to detect an age effect because of their inclusion of younger children. Our study consisted of fewer individuals and because we only studied individuals between the ages of 12 and 30, we may have experienced age-related attenuation. However, three other studies, two of adolescents (Logan et al. 2012; Memari et al. 2012), and one of adolescents and adults (Esbensen et al., 2009), did report an association between age and polypharmacy, and their sample sizes were similar to ours. A lack of association between gender and polypharmacy is consistent with findings among children and adolescents with ASD (Coury et al. 2012; Memari et al., 2012; Spencer et al. 2013). No other studies considered the association between polypharmacy and autism diagnosis, and only one other study considered the association between polypharmacy and ID (Spencer et al., 2013). Consistent with findings of the current study, Spencer and colleagues (2013) did not

report an association between ID and polypharmacy. The finding of no association between psychotropic polypharmacy and autism diagnosis or intellectual disability supports the notion that polypharmacy is an issue for adolescents and young adults with ASD across levels of cognitive functioning and autism severity, and is not a concern unique to lower functioning individuals. While the reasons for prescribing multiple psychotropic medications and the ways in which they are monitored may differ among these individuals, polypharmacy can be a concern across the spectrum.

Two clinical variables were associated with psychotropic polypharmacy in the multivariate analyses: history of hurting others and presence of an additional psychiatric diagnosis. One would expect that individuals with comorbid mental health problems would be more likely to be prescribed multiple medications than those without. This finding was also observed in a study of children with ASD, where children with co-occurring conditions had higher odds of polypharmacy (Spencer et al. 2013). The finding that hurting others was associated with psychotropic polypharmacy is consistent with our previous work with an adult sample, the majority of whom were no longer living with family (Lake et al. 2012), although there is no systematic evidence to indicate that multiple psychotropic medications, particularly medications from the same class, are more effective than one psychotropic medication in addressing aggressive behaviour. It would be important to examine whether parents think that multiple psychotropic medications are in fact working, since some of these medications both individually or taken together, can have adverse or paradoxical side effects, and in some cases, may worsen the behaviours they are prescribed to treat (Bradley and Lofchy 2005; Myers 2007).

Parent Variables

Parent crisis, parent burden, and the use of family counseling services were all associated with psychotropic polypharmacy at the bivariate level, and parent burden remained a significant predictor after adjusting for clinical and service factors. This means that even when controlling for severity of autism symptoms, presence of ID, and child behaviour or mental health problems, parents' perception of their difficulty caring for their child was still an important predictor of polypharmacy. The relationship between parent burden and increased psychotropic medication use may be influenced by a third mediating variable (e.g., aggressive behaviour). For example, when faced with aggressive behaviour, parents may have a greater sense of burden and be more likely to use multiple medications. It is well known that parents report greater distress in the presence of child behaviour and mental health problems (Cadman et al. 2012; Kring et al. 2008; Lin 2011; Schieve et al. 2007), and that mental health problems are associated with greater medication use. It remains an intriguing possibility that parent burden may influence the decision to medicate, but more refined measures of aggressive behaviour, behaviours targeted with medication, and the decision to medicate are required to better understand the inter-relationships between these child and parent variables. Whatever the reason, parent burden was elevated for parents' who had a child using multiple medications, suggesting that supporting parents in these circumstances may be an important target for treatment and education.

Service Variables

Among service variables, only therapy use predicted psychotropic polypharmacy. This finding suggests that the majority of adolescents and young adults prescribed

multiple psychotropic medications are doing so while accessing and receiving adjunct therapy services and supports (e.g., behaviour therapy, counseling). These results are similar to what has been found among the general youth population, where 68% of youth prescribed psychotropic medication also receive concurrent therapy (Harris et al. 2012). While it is positive that pharmacological treatments are not being used in lieu of non-pharmacological treatments for the majority of individuals, just over one third (36%) of those taking two or more psychotropic medications, were not receiving any additional therapy. This is particularly concerning given our knowledge that behaviour therapy in addition to psychiatric treatment is more effective than psychiatric treatment alone (Aman et al. 2009; Hassiotis et al. 2009; Kaplan and McCracken 2012; Myers and Plauche-Johnson 2007; Frazier et al. 2010). Although there is a need for more methodologically rigorous studies examining the effectiveness of psychosocial interventions for the treatment of aggression among persons with ASD, a number of studies demonstrate its treatment effectiveness (Brosnan & Healy, 2011; Campbell, 2003; Foxx, 2008)

This study is subject to a number of limitations. First, findings were based on parent report, and we did not have access to corroborating sources to validate diagnoses or medications. However, only individuals with an SCQ score at or above the recommended research cutoff (≥ 12) (Brooks & Benson 2013) were included in these analyses. It is possible that some individuals in this study would not meet full DSM-V criteria for ASD; however, previous studies suggest that parent-reported ASD diagnoses produce prevalence estimates comparable to population-based studies using validated medical records or diagnostic tools (CDC 2012; 2013; Kogan et al. 2009). While we recognize

that our sample may not be representative of all individuals with ASD, most individuals with ASD tend to reside with their parents well into adulthood (Howlin and Moss 2012), thus findings from parent report surveys have considerable value in understanding adolescents and adults with ASD. Similarly, despite its constraints, a number of studies have used similar survey-based methods to study this population (Blumberg et al. 2013; Mazurek et al. 2011; Montes and Halterman 2007), including the 2011-2012 National Survey of Children's Health (CDC 2013) and the 2011-2012 National Health Interview Survey (CDC 2012).

Second, our measure of hurting others was not refined enough to directly address whether hurting others was a precursor to medication prescribing. Third, data collection in the current study did not consider a medication overlap period, which may have resulted in an overestimate of psychotropic polypharmacy rates if on the date medications were recorded the individual was being weaned off one medication while another was being introduced (Chen et al. 2011). Fourth, it is challenging to tease apart the relationship between predictors and outcomes based on the cross-sectional nature of the data in the current study. More refined study of these constructs and longitudinal data are needed.

Conclusions

Despite these limitations, findings from the current study have a number of important implications. Our results contribute to the literature on psychotropic medication use in adolescents and young adults with ASD, and confirm that this subgroup is a highly medicated population. Findings also suggest that the factors associated with psychotropic polypharmacy are complex and multifaceted. It may not

simply be the clinical variables related to the child which lead to multiple psychotropic medication use, but rather the interplay between child, parent, and service factors. While there are many circumstances where polypharmacy is a necessary and appropriate sign of good psychiatric care, identification of risk factors for psychotropic polypharmacy could inform the development of alternative interventions that complement or replace pharmacological treatments. This may include patient-centered supports for adolescents or young adults with ASD who present with comorbid mental health problems or a history of hurting others, as well as supports for parents of these individuals. Going forward, it will be important to study whether psychotropic medications are having their intended benefit among individuals with ASD and how these medications impact parent burden over time. There is also a need for an in-depth understanding of the choice to medicate from the perspective of parents and prescribing healthcare providers, as well as how these different factors come into play throughout the decision-making process. Findings from this study highlight the need to find ways to support parents who have children using multiple psychotropic medications whom appear to be highly burdened.

Clinical Significance: This is the first study of adolescents and young adults with ASD to examine both demographic and clinical variables associated with multiple psychotropic medication use, and to consider the relative influence of parent and service factors. Findings suggest that the factors associated with psychotropic polypharmacy are complex and multifaceted. In our study, it is not simply the clinical variables related to the child which lead to multiple psychotropic medication use, but rather the interplay between child, parent, and service factors. Clinically, identification of risk factors for psychotropic polypharmacy could inform the development of alternative interventions that complement pharmacological treatments. This may include patient-centered supports for adolescents or young adults with ASD who present with comorbid mental health problems or a history of hurting others, as well as supports for parents of these individuals.

Disclosures: None for any author

Acknowledgments The authors thank the Canadian Institutes of Health Research (funding reference number 102677) and the Centre for Addiction and Mental Health Postdoctoral Fellowship Award for funding this research study. The authors thank the project scientists and staff as well as participating agencies for their involvement. They also thank Melissa Paquette-Smith and Alex Milovanov for assistance.

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